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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/880,654	06/13/2001	Leanna M. Levine	2842/3	7335
26648	7590	01/15/2004		
PHARMACIA CORPORATION GLOBAL PATENT DEPARTMENT POST OFFICE BOX 1027 ST. LOUIS, MO 63006			EXAMINER WINKLER, ULRIKE	
			ART UNIT	PAPER NUMBER
			1648	

DATE MAILED: 01/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/880,654

Applicant(s)

LEVINE ET AL.

Examiner

Ulrike Winkler

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 November 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-11 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-11 is/are rejected.
- 7) ☒ Claim(s) 10 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
- a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

The Amendment filed November 13, 2003 in response to the Office Action of November August 11, 2003 is acknowledged and has been entered. Claims 1-11 are pending and are currently being examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 112

The rejection of claim 10 **is maintained**. The claim recites the limitation "Abu" in the claim, according to the abbreviations allowed see MPEP 2422 the abbreviation Abu is 2-Aminobuteric acid. There is insufficient antecedent basis for this limitation in the claim since claim 3 does not recite 2-aminobuteric acid as one of the enumerated groups. Amending the claim so it is depends from claim 2 would obviate this rejection as Abu is an aminoalkylcarboxylic acid. Applicant's arguments have been fully considered but are not persuasive, the argument is that claim 3 contains all the limitations of claim 2 and therefore claim 10 is properly dependent on claim 3. CFR 1.75(c) requires the dependent claim to further limit a preceding claim, in this instance claim 3 is a proper depend claim as if further limits claim 2. Claim 3 as written is limited to the compounds cited in the claim of which 2-aminobuteric acid is not one of the compounds listed, therefore the rejection of claim 10 is maintained for not having sufficient antecedent basis to depend on claim 3.

Claim Rejections - 35 USC § 112

The rejection of claims 1 and 11 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention **is maintained**. The claims are indefinite in that they do not set forth clearly the method steps to carry out “a method of determining the activity of a protease” or “a method of identifying a compound which inhibit a protease” because the nature and the endpoint(s) of claimed methods are ambiguous and unclear.

Applicants argue that measuring the fluorescent polarization is the endpoint. As the claim is written the substrate, protease compound and the florescent measurement are all taken at the same time. The method step does not have a resolution step which indicates what change in the fluorescence activity will be indicative of being a protease inhibitor. For example, “wherein the constant in the P value of the fluoresce measurement would indicate that the compound prevents the protease from cleaving the substrate and is thereby an inhibitor of the protease”. As the claims is written there is an absence or lack of clarity as to critical or resolutions steps which reads back on the preamble of the claimed methods. Correction is required.

Claim Rejections - 35 USC § 103

The rejection of claim 10 under 35 U.S.C. 103(a) as being obvious **is withdrawn**, it is noted that the SEQ ID NO 4 of the prior art Heath et al. (U.S. Pat. No. 5,235,039, IDS) contains a Gln in SEQ ID NO:4 and not a Gly as found in the instant claim 10. There is no teaching in the prior art that would have indicated to make such a substitution in the enzyme substrate.

The rejection of claims 1-9 and 11 under 35 U.S.C. 103(a) as being obvious over Heath et al. (U.S. Pat. No. 5,235,039, IDS), Bromberg (U.S. Pat. No. 4,203,670) and Maeda (Analytical Biochemistry 1979, IDS) in view of Welch et al. (PNAS 1991, IDS) or Blakeslee et al. (Journal of Immunological Methods, 1976) is **maintained** for reasons of record.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Furthermore, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants arguments are that neither Heath et al. or Bromberg teach a peptidic substrate, that Meada does not teach the applicability of the substrate being bound to an anchor and Welch does not disclose techniques applicable to the high throughput capability claimed in the instant invention. Applicants' arguments have been fully considered but they fail to persuade. In this case, Heath et al. do teach a peptidic substrate for an HIV protease that comprises biotin on one side of the scissile bond and FITC on the other side of the scissile bond. Heath et al. teaches the step of binding the substrate onto a solid surface while incubating the substrate in the presence of a test compound and a protease. Applicants' argument is that it would have been unobvious at

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the time of the invention to apply a fluorescence polarization detection as taught by Bromberg or Maeda to the bound substrate taught by Heath et al. Applicants argument is not convincing because Maeda teach that the fluorescent polarization works by attaching the fluorescent molecule to a large substrate molecule which serves to hold the fluorescent molecule stable [i.e. minimizing Brownian motion] and thereby does not allow the fluorescent detection molecule to tumble freely in solution which would cause a decrease in the measured P-value. This same stabilization is achieved by the attachment of the substrate to the solid surface as taught by Heath et al. The method set out by Heath et al. utilizes the liberated fluorescent molecule by adding the additional step of separating the molecule before reading the fluorescence. Maeda teaches the procedure of using fluorescent polarization to determine the difference the cleaved substrate over time in a single cuvette, the procedure has the advantage that it does not require any further processing such as separation, precipitation or centrifugation.

It remains the position of the Office that it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize known substrates for the detection of protease activity and apply the fluorescence polarization technique to determine substrate cleavage which can be obtained directly from the reaction mixture in a single cuvette as taught by Maeda. It would have been obvious to one of ordinary skill in the art at the time the invention was made utilize the substrate construction as taught by Heath et al. and apply them to the peptide substrates taught by Welch et al. One would have been motivated to do this in order to develop a single step assay for herpes virus proteases. Optimizing experimental conditions, including the addition of spaces between the amino acid and the binding group or fluorescing group, choosing the fluorescing group so that it minimizes quenching and optimizes signal

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output, falls within the skills of an ordinary artisan. Blakeslee et al. teaches that DTAF and FITC have identical properties, because of the lower cost involved with DTAF one having ordinary skill in the art would have been motivated to substitute DTAF for FITC in the substrate taught by Heath et al. Therefore, the instant invention is obvious over Heath et al., Maeda et al. and Bromberg in view of Welch et al. or Blakeslee et al.

Claim Objections

Claim 10 is objected to because of the following informalities: The claim is objected to because it depends on a rejected claim. The claim would be allowable if rewritten in independent form. Appropriate correction is required.

Conclusion

Claims 1-11 are rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

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however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294, please note after February 2004 the telephone number will change to 571-272-0912. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The official fax phone number for the organization where this application or proceeding is assigned is 703-872-9306; for informal communications please use 703-746-3162, please note after February 2004 the fax phone number will change to 571-273-0912

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.


ULRIKE WINKLER, PH.D.
PATENT EXAMINER 1/9/04